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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,099	10/31/2003	Dale B. Schenk	015270-008930US	7805

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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,099	SCHENK ET AL.	
	Examiner	Art Unit	
	Michelle Horning	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-13,54 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 9-13, 54-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to an RCE filed 11/01/2007. The status of the claims is as follows: claims 1-6, 9-13 and 54-55 are under current examination.

Applicants' arguments have been considered and are found persuasive. Thus, the following rejection has been withdrawn:

1. 35 USC 103 (Yoshimoto et al, Wakabayashi et al, Que et al and Cleland et al).

Information Disclosure Statement

The IDS has been considered in its entirety.

Specification

The use of multiple trademarks has been noted in this application, including ACCEL, MEDIPAD and ATTO-PHOS. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "good manufacturing conditions" in claim 54 is a relative term which renders the claim indefinite. The term

"good" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9-13 and 54-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mere composition comprising some immunogenic agents, does not reasonably provide enablement for a pharmaceutical composition comprising any and all possible agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors.

Nature of the invention. The claims are drawn to a pharmaceutical composition comprising any and all possible agents that elicits an immunogenic response to alpha-synuclein and an adjuvant.

State of the prior art. The specification provides the following on pages 3-4 regarding the state of the prior art:

> [0008] The neuritic plaques that are the classic pathological hallmark of AD contain beta amyloid (AB) peptide and non-beta amyloid component (NAC) peptide. AB is derived from a larger precursor protein termed amyloid precursor protein (APP). NAC is derived from a larger precursor protein termed the non-beta amyloid component of APP, now more commonly referred to as alpha-SN. NAC comprises amino acid residues 60-87 or 61-95 of alpha-SN. Both AB and NAC were first identified in amyloid plaques as proteolytic fragments of their respective full-length proteins, for which the full-length cDNAs were identified and cloned.

[0009] Alpha-SN is part of a large family of proteins including beta- and gamma- synuclein and synoretin. Alpha-SN is expressed in the normal state associated with synapses and is believed to play a role in neural plasticity, learning and memory. Mutations in human (h) alpha-SN that enhance the aggregation of alpha-SN have been identified (Ala30Pro and Ala53Thr) and are associated with rare forms of autosomal dominant forms of PD. The mechanism by which these mutations increase the propensity of alpha-SN to aggregate are unknown.
[0010] Despite the fact that a number of mutations can be found in APP and alpha-SN in the population, most cases of AD and PD are sporadic. The most frequent sporadic forms of these diseases are associated with an abnormal accumulation of AI3 and alpha-SN, respectively. However, the.reasons for over accumulation of these proteins is unknown. AB is secreted from neurons and accumulates in extracellular amyloid plaques. Additionally AB can be detected inside neurons. Alpha-SN accumulates in intraneuronal inclusions called LBs. Although the two proteins are typically found together in extracellular neuritic AD plaques, they are also occasionally found together in intracellular inclusions.
[0011] The mechanisms by which alpha-SN accumulation leads to neurodegeneration,and the characteristics symptoms of PD are unclear. However, identifying the role of factors promoting and/or blocking alpha-SN aggregation is critical for the understanding of LBD pathogenesis and development of novel treatments for its associated disorders. Research for. identifying treatments has been directed toward searching for compounds that reduce alpha- SN aggregation (Hashimoto, et al.) or testing growth factors that will promote the regeneration and/or survival of dopaminergic neurons, which are the cells primarily affected (Djaldetti et al., New therapies for Parkinson's disease, J. Neurol (2001) 248:357-62; Kirik et al., Long-term rAA V-mediated gene transfer of GDNF in the rat Parkinson's model: intrastriatal but not intranigral transduction promotes functional regeneration in the lesioned nigrostriatal system, J. Neurosci (2000) 20:4686-4700). Recent studies in a transgenic mouse model of AD have shown that antibodies against AI3 1-42 facilitate and stimulate the removal of. amyloid from the brain, improve AD-like pathology and resulting in improve cognitive performance (Schenk et al., Immunization with amyloid-fl attenuates Alzheimer-disease-like pathology in PDAPP mouse, Nature (1999) 408:173-177; Morgan et al., A-beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease, Nature (2000) 408:982-985; Janus et al., A-beta peptide immunization reduces behavioral impairment and plaques in a model of Alzheimer's disease, Nature (2000) 408:979-82). In contrast to the extracellular amyloid plaques found in the brains of Alzheimer's patients, Lewy bodies are intracellular, and antibodies do not typically enter the cell.

Breadth of the claims. The claims are broad in that they encompass any and all possible agents that are effective in eliciting an immunogenic response alpha-synuclein. It is further noted that the agent may be any immunogenic fragment of alpha-synuclein and a fragment may be considered a dipeptide that is not necessarily unique to alpha-synuclein.

Guidance in the specification. With respect to the claimed "pharmaceutical composition", the specification provides following recitation: "In prophylactic applications, pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of a LBD in regime comprising an amount and

frequency of administration of the composition or medicament sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including physiological, biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. In therapeutic applications, compositions or medicates are administered to a patient suspected of, or already suffering from such a disease in a regime comprising an amount and frequency of administration of the composition sufficient to cure, or at least partially arrest, the symptoms, of the disease (physiological, biochemical, histologic and/or behavioral), including its complications and intermediate pathological phenotypes in development of the disease" (see paragraph 222). The working examples are discussed below and it is not clear how they satisfy the above recitation regarding a "pharmaceutical composition" as described by the Applicants.

The specification fails to provide guidance for what an immunogenic fragment is. As noted above, a fragment may be a dipeptide that is not necessarily unique to an alpha-SN protein or the homologous regions of NAC. Of note, the alpha-SN protein is 140 residues in length. See examples below in which only the full-length alpha-SN is used in immunization of mice *in vitro*.

Working examples. Working examples show that mice can produce anti-alpha-SN antibodies following immunization of the full-length alpha-SN. Neuropathologically analysis showed that mice which produced a high titer of antibodies had a marked decrease in the size of the synuclein incusions (see page 59). Secondly, the inventors submit that peripherally administered antibodies cross the blood brain barrier and lead

to clearing of synuclein deposits (see page 60 and Figure 2). It appears that the Applicants are suggesting a correlation between antibody titers and the size of the inclusion. According to Table 1, however, the data fails to show this; see column under Syn (+) inclusions/mm2. There is no difference between the groups, each of which demonstrates varied titers. *Applicant is invited to address this issue with respect to a "pharmaceutical composition" as claimed.* Example 2 presents data in which alpha-SN antibody results in the clearance of synuclein associated with the cellular membrane in cell lines; it is noted here that the specification discloses that Lewy bodies are *intracellular* within brain tissue (see paragraph 11). Example 3 teaches the prophylactic and therapeutic efficacy of alpha-SN immunization and how this will be accessed behaviorally and neuropathologically. No data is provided, only the underlying theory which will be applied futuristically. Example 4 provides different regions of alpha-SN protein used for immunization; it is describes 9 different immunogens but it only provides 4, two of which are homologous to NAC regions. No data is provided here. Example 5 is drawn to the injection of antibodies (not immunogens) to alpha-SN in mice and the titers are monitored. Example 6 reveals that in some types of mice, immunization with Abeta 1-42 also clears synuclein deposits in addition to Abeta deposits.

Predictability in the art. There is no way no could predict the successful immunogenic fragments of an alpha-SN which would lead to a successful pharmaceutical composition. As noted above, the alpha-SN is 140 residues in length and the specific protein regions as well as their lengths would not predictable for an

immunogen to the ordinary artisan. Additionally, it is not known whether the resulting antibodies can even penetrate the cellular membrane and have access to the intracellular Lewy bodies.

Amount of experimentation necessary. Bradbury (2005) discusses the works by the inventors of the instant application. The following are recitations taken from this reference and they demonstrate undue experimentation. "'But we found that antibodies produced in a mouse PD model by immunization with human alpha-synuclein both recognized abnormal alpha-synuclein associated with neuronal membranes and targeted it for destruction through the lysosomal degradation pathway.' These results, notes Elan's Chief Scientific Officer and co-author Dale Schenk, offer a new and unexpected strategy for the treatment of PD' although *any clinical application is likely to be some years down the line*" (see page 1075, emphasis added). Separately, the reference provides this recitation regarding this invention, "However, he cautions, *many hurdles must be overcome before clinical application of the approach can be considered. Overcoming these hurdles will require, among other things, broader analyses of immune system response to vaccination and the testing of antibody responses in other models of PD*" (see page 1075). Lastly, the author provides the following: "Before immunization against alpha-synuclein can be studied clinically,' she notes, 'we need to understand exactly how the antibodies get into the brain'" (see page 1076). As revealed by the above recitation, much work is crucial in order for the claimed composition to be dubbed a "pharmaceutical".

Given the reasons above, it would require much undue experimentation for one of ordinary skill in the art to practice the full scope of the invention as claimed.

Conclusion

NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michelle Horning whose telephone number is 571-272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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